

Rhinitis and sinusitis

Mark S. Dykewicz, MD,^a and Daniel L. Hamilos, MD^b Winston-Salem, NC, and Boston, Mass

Rhinitis and sinusitis are among the most common medical conditions and are frequently associated. In Western societies an estimated 10% to 25% of the population have allergic rhinitis, with 30 to 60 million persons being affected annually in the United States. It is estimated that sinusitis affects 31 million patients annually in the United States. Both rhinitis and sinusitis can significantly decrease quality of life, aggravate comorbid conditions, and require significant direct medical expenditures. Both conditions also create even greater indirect costs to society by causing lost work and school days and reduced workplace productivity and school learning. Management of allergic rhinitis involves avoidance, many pharmacologic options, and, in appropriately selected patients, allergen immunotherapy. Various types of nonallergic rhinitis are treated with avoidance measures and a more limited repertoire of medications. For purposes of this review, *sinusitis* and *rhinosinusitis* are synonymous terms. An acute upper respiratory illness of less than approximately 7 days' duration is most commonly caused by viral illness (viral rhinosinusitis), whereas acute bacterial sinusitis becomes more likely beyond 7 to 10 days. Although the mainstay of management of acute bacterial sinusitis is antibiotics, treatment of chronic sinusitis is less straightforward because only some chronic sinusitis cases have an infectious basis. Chronic rhinosinusitis (CRS) has been subdivided into 3 types, namely CRS without nasal polyps, CRS with nasal polyps, and allergic fungal rhinosinusitis. Depending on the type of CRS present, a variety of medical and surgical approaches might be required. (J Allergy Clin Immunol 2010;125:S103-15.)

Key words: Rhinitis, sinusitis, rhinosinusitis, allergic, fungal sinusitis, nasal polypsis

Rhinitis and sinusitis are among the most common medical conditions and are frequently associated.¹⁻⁴ An estimated 10% to 25% of the population in Western societies has allergic rhinitis.^{1,2}

From ^aAllergy and Immunology Unit, Section of Pulmonary, Critical Care Allergy and Immunologic Diseases, Department of Internal Medicine, Center for Human Genomics and Personalized Medicine Research, Wake Forest University School of Medicine, Winston-Salem, and ^bthe Division of Rheumatology, Allergy & Immunology, Massachusetts General Hospital/Harvard Medical School, Boston.

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Reprint requests: Mark S. Dykewicz, MD, Center for Human Genomics and Personalized Medicine Research, Wake Forest University School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157. E-mail: dykewicz@wfubmc.edu. 0091-6749/\$36.00

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Abbreviations used

| | |
|---------|---|
| ABRS: | Acute bacterial rhinosinusitis |
| AERD: | Aspirin-exacerbated respiratory disease |
| AFRS: | Allergic fungal rhinosinusitis |
| AR: | Allergic rhinitis |
| CRS: | Chronic rhinosinusitis |
| CRScNP: | Chronic rhinosinusitis with nasal polypsis |
| CRSsNP: | Chronic rhinosinusitis without nasal polypsis |
| CT: | Computed tomography |
| FDA: | US Food and Drug Administration |
| FESS: | Functional endoscopic sinus surgery |
| INS: | Intranasal corticosteroids |
| LTRA: | Leukotriene receptor antagonist |
| NARES: | Nonallergic rhinitis with eosinophilia syndrome |
| PAR: | Perennial allergic rhinitis |
| PRN: | As required |
| SAR: | Seasonal allergic rhinitis |
| URI: | Upper respiratory tract infection |

Sinusitis affects an estimated 31 million persons annually in the United States.³ Both rhinitis and sinusitis can significantly decrease quality of life, aggravate comorbid conditions, and require significant direct medical expenditures. Both conditions also create even greater indirect costs to society by causing lost work and school days, as well as reduced workplace productivity and school learning.

For the purposes of this review, *sinusitis* and *rhinosinusitis* are synonymous terms.

RHINITIS Background

Although semantically, the term rhinitis implies inflammation of the nasal mucous membranes, inflammatory cell infiltrates are not characteristic of all disorders considered to be rhinitis. As a clinical term, rhinitis refers to a heterogeneous group of nasal disorders characterized by 1 or more of the following symptoms: sneezing, nasal itching, rhinorrhea, and nasal congestion.¹ Rhinitis can be caused by allergic, nonallergic, infectious, hormonal, occupational, and other factors.^{1,2} Allergic rhinitis is the most common type of chronic rhinitis, but 30% to 50% of patients with rhinitis have nonallergic triggers. Preliminary data suggest that 44% to 87% of patients with rhinitis might have mixed rhinitis, a combination of allergic and nonallergic rhinitis.^{1,2,5} Worldwide, the prevalence of allergic rhinitis continues to increase. Studies suggest that seasonal allergic rhinitis (hay fever) is found in approximately 10% to 20% of the general population,^{1,2} with an even greater prevalence in children. Overall, allergic rhinitis affects 30 to 60 million subjects in the United States annually.^{1,6} Severe allergic rhinitis has been associated with diminished quality of life, disordered sleep (in as many as 76% of patients), obstructive sleep apnea, and impairment in work performance.^{1,2} In addition, rhinitis can contribute to sinusitis (see the section below on Sinusitis, comorbidities, and allergic rhinitis) and is frequently associated with asthma.

Pathogenesis

Nasal anatomy and physiology. The nasal cavity (Fig 1) is divided by the nasal septum, which is composed of bone more proximally and cartilage more distally. The inferior, middle, and superior turbinates in the nasal cavity promote air filtration, humidification, and temperature regulation. The nasal cavity and turbinates are lined with mucosa comprised of pseudostratified columnar ciliated epithelium that overlies a basement membrane and the submucosa (lamina propria). The submucosa consists of serous and seromucous nasal glands, nerves, extensive vasculature, and cellular elements. Overlying the nasal epithelium is a thin layer of mucus that dynamically moves by means of ciliary action to the posterior nasopharynx. Infections (viral or bacterial) and allergic inflammation impair mucociliary clearance. Because nasal tissues are highly vascular, vascular changes can lead to significant nasal obstruction. Vasoconstriction and consequent decreases in nasal airway resistance result from sympathetic nerve stimulation. Parasympathetic nerve stimulation promotes secretion from nasal airway glands and nasal congestion. The nasal mucosa also contains nerves of the nonadrenergic noncholinergic system. Neuropeptides from the latter nerves (substance P, neurokinin A and K, and calcitonin gene-related peptide) are thought to play some role in vasodilatation, mucus secretion, plasma extravasation, neurogenic inflammation, and mast cell nerve interactions, but the relative clinical importance of neuropeptides needs further definition.⁷

Allergic rhinitis

Pathophysiology. Common allergens causing allergic rhinitis include proteins and glycoproteins in airborne dust mite fecal particles, cockroach residues, animal danders, molds, and pollens. On inhalation, allergen particles are deposited in nasal mucus, with subsequent elution of allergenic proteins and diffusion into nasal tissues. In addition, small-molecular-weight chemicals in occupational agents or drugs can act as haptens that react with self-proteins in the airway to form complete allergens. Evidence extrapolated from asthma studies suggests that once in nasal tissues, common aeroallergens not only undergo antigen processing to elicit allergen-specific allergic responses but also promote development of allergic airway disease through their inherent properties. For example, protease activities of several common aeroallergens can facilitate allergen access to antigen-presenting cells by cleaving tight junctions in the airway epithelium and activation of protease-activated receptors on epithelial cells.⁸ Activated epithelial cells then produce cytokines, chemokines, and thymic stromal lymphopoietin, which interact with interepithelial and subepithelial dendritic cells to skew T-cell development and adaptive allergic sensitization. The house dust mite allergen Der p 2 mimics MD-2, the LPS-binding component of the Toll-like receptor 4 signaling complex,² and facilitates Toll-like receptor 4 signaling and airway T_H2-type inflammation.⁹

In the nose allergens are processed by antigen-presenting cells (dendritic cells expressing CD1a and CD11c and macrophages) in the nasal epithelial mucosa, with subsequent presentation of allergenic peptides by MHC class II molecules to T-cell receptors on resting CD4⁺ T lymphocytes in regional lymph nodes. With costimulatory signals, allergen-stimulated T cells proliferate into T_H2-biased cells that release IL-3, IL-4, IL-5, IL-13, and other cytokines. These cytokines then lead to a cascade of events that promote B-cell isotype switching with subsequent local and

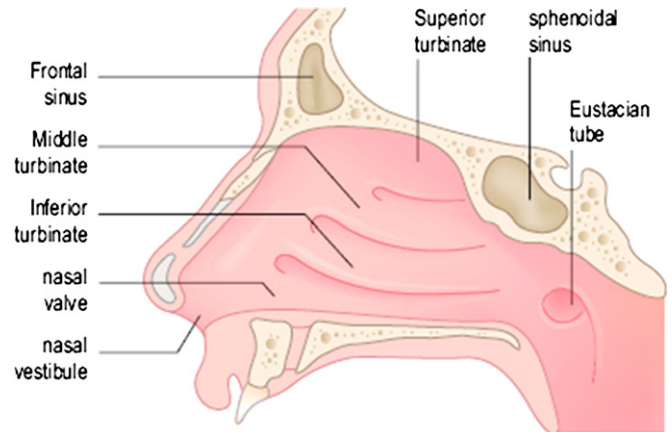


FIG 1. Nasal anatomy. Reprinted with permission from Dykewicz MS. Rhinitis and sinusitis. In: Rich RR, Fleischer TA, Shearer WT, Schroeder HW Jr, Frew AJ, Weyand CM, editors. *Clinical Immunology*. 3rd ed. London: Mosby Elsevier; 2008. p. 626-39.

systemic production of allergen-specific IgE antibody production by plasma cells, eosinophilic infiltration into the nasal epithelium and mucosa, and mast cell proliferation and infiltration of airway mucosa.

Early/immediate allergic response. Within minutes of inhalation of allergen in sensitized subjects, deposited allergens are recognized by IgE antibody bound to mast cells and basophils, causing degranulation and release of preformed mediators, such as histamine and tryptase, and the rapid *de novo* generation of mediators, including cysteinyl leukotrienes (leukotrienes C₄, D₄, and E₄) and prostaglandin D₂. Mediators cause plasma leakage from blood vessels and dilation of arteriovenous arteriole venule anastomoses, with consequent edema, pooling of blood in the cavernous sinusoids (the principal cause of the congestion of allergic rhinitis), and occlusion of the nasal passages. Mediators also stimulate active secretion of mucus from glandular and goblet cells. Histamine elicits itching, rhinorrhea, and sneezing, whereas other mediators, such as leukotrienes and prostaglandin D₂, likely have more important roles in the development of nasal congestion. Stimulation of sensory nerves results in the perception of nasal congestion and itching and can provoke systemic reflexes, such as sneezing paroxysms.^{1,10}

Late-phase response. Mediators and cytokines released during the early phase set off a cascade of events over the ensuing 4 to 8 hours that lead to an inflammatory response called the late response. Although clinical symptoms during the late phase might be clinically similar to those of the immediate reaction, nasal congestion is more prominent. The cysteinyl leukotrienes also play an active role in recruitment of inflammatory cells. Mediators and cytokines released during the early response act on post-capillary endothelial cells to promote expression of adhesion molecules, such as intercellular adhesion molecule 1, E-selectin, and vascular cell adhesion molecule 1, that promote adherence of circulating leukocytes, such as eosinophils, to endothelial cells. Factors with chemoattractant properties, such as IL-5 for eosinophils, promote the infiltration of the superficial lamina propria of the mucosa with many eosinophils, some neutrophils and basophils, and eventually CD4⁺ (T_H2) lymphocytes and macrophages.¹ These cells become activated and release more mediators, which in turn activate many of the proinflammatory reactions seen in the immediate response.

Priming effect. The amount of allergen necessary to elicit an immediate response becomes less when allergen challenges are given repeatedly, a phenomenon called the priming effect.^{1,11} During ongoing, prolonged allergen exposure and repeated late-phase/inflammatory responses, the nasal mucosa becomes progressively more inflamed and responsive to allergen. Clinically, the priming effect can explain why patients might have increasing symptoms despite decreasing aeroallergen levels as a season progresses and also provides the rationale for initiating effective anti-inflammatory rhinitis therapies before a pollen season or before other chronic or repetitive aeroallergen exposures. In addition, the priming effect from allergen is also associated with mucosal hyperresponsiveness to nonantigenic triggers, such as strong odors and cigarette smoke.

Associated nonnasal symptoms. Allergic rhinitis is often accompanied by allergic conjunctivitis (a complex sometimes referred to as allergic rhinoconjunctivitis) that results in conjunctival injection and chemosis and symptoms of itchy eyes and tearing.¹ The prevalence and severity of conjunctival symptoms associated with allergic rhinitis vary with several factors, but one study found allergic conjunctivitis symptoms in more than 75% of patients with seasonal allergic rhinitis.¹² Sensitivity to pollens is more frequently associated with ocular symptoms than is sensitivity to house dust mites. Itching of the ears and throat can also be associated with allergic rhinitis.

Association with asthma. Allergic asthma and rhinitis are comorbid conditions that are associated pathophysiologically and epidemiologically.^{1,2} Both are airway diseases in which IgE antibody sensitization to aeroallergens is a prominent feature. There is some evidence that systemic trafficking of inflammatory cells from local inflammation in one portion of the respiratory tract can induce inflammatory changes in the other, with one example being that segmental bronchial allergen challenge in patients with allergic rhinitis has been shown to result in both bronchial and nasal inflammatory responses.¹³ Treatment with intranasal corticosteroids in patients with allergic asthma and rhinitis has been shown to prevent the seasonal increase in bronchial hyperreactivity and to reduce existing bronchial hyperreactivity.^{1,14,15} More than 80% of persons with allergic asthma have allergic rhinitis, and allergic rhinitis is a clear risk factor for the eventual development of asthma.^{1,2} Guidelines recommend that patients with persistent allergic rhinitis should be evaluated for asthma and patients with asthma should be evaluated for rhinitis.^{1,2}

Differential diagnosis, including forms of nonallergic rhinitis. Some of the classic symptoms of allergic rhinitis (rhinorrhea, nasal congestion, sneezing, and nasal itching) overlap with symptoms associated with forms of nonallergic rhinitis (Table I) and various anatomic abnormalities of the upper airway (Table II), sometimes making it difficult to distinguish between these disorders on the basis of history alone.

Nonallergic rhinitis without eosinophilia. Sometimes termed *idiopathic rhinitis*,² this manifests as chronic nasal symptoms not caused by allergic or infectious processes. Symptoms are nasal obstruction, increased secretions, or both, with sneezing and pruritus being less common. This clinical presentation is likely caused by a heterogeneous group of disorders with a pathogenesis that is incompletely understood. *Vasomotor rhinitis* is a term that is sometimes used synonymously with the term *nonallergic rhinitis without eosinophilia* but sometimes can more specifically connote nasal symptoms that occur in response to environmental

TABLE I. Types of rhinitis

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|---|
| I. Allergic rhinitis |
| II. Nonallergic rhinitis |
| A. Vasomotor rhinitis |
| 1. Irritant triggered (eg, chlorine) |
| 2. Cold air |
| 3. Exercise (eg, running) |
| 4. Undetermined or poorly defined triggers |
| B. Gustatory rhinitis |
| C. Infectious |
| D. NARES |
| III. Occupational rhinitis |
| A. Caused by protein and chemical allergens; IgE mediated |
| B. Caused by chemical respiratory sensitizers; immune mechanism uncertain |
| C. Work-aggravated rhinitis |
| IV. Other rhinitis syndromes |
| A. Hormonally induced |
| 1. Pregnancy rhinitis |
| 2. Menstrual cycle related |
| B. Drug induced |
| 1. Rhinitis medicamentosa |
| 2. Oral contraceptives |
| 3. Antihypertensive and cardiovascular agents |
| 4. Aspirin/NSAIDs |
| 5. Other drugs |
| C. Atrophic rhinitis |
| D. Rhinitis associated with inflammatory-immunologic disorders |
| 1. Granulomatous infections |
| 2. Wegener granulomatosis |
| 3. Sarcoidosis |
| 4. Midline granuloma |
| 5. Churg-Strauss syndrome |
| 6. Relapsing polychondritis |
| 7. Amyloidosis |

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NSAIDs, Nonsteroidal anti-inflammatory drugs.

conditions, such as changes in temperature or relative humidity, odors (eg, perfumes or cleaning materials), passive tobacco smoke, alcohol, sexual arousal, and emotional factors. Such hyperreactivity to nonallergic triggers is not mediated by increased neural efferent traffic to the blood vessels supplying the nasal mucosa and can also occur in allergic rhinitis, when the term *mixed rhinitis* is applied.^{1,2}

Nonallergic rhinitis with eosinophilia syndrome. Nonallergic rhinitis with eosinophilia syndrome (NARES) is characterized by perennial nasal symptoms (particularly nasal congestion), sneezing paroxysms, profuse watery rhinorrhea, nasal pruritus, and occasional loss of smell.^{1,2} Nasal smears demonstrate eosinophils (inconsistently defined as >5% to >20%),^{16,17} as in allergic rhinitis, but patients lack evidence of allergic disease based on skin testing or serum levels of IgE to environmental allergens. However, similar to histologic findings in patients with allergic rhinitis, mast cells with bound IgE and increased tryptase levels have been found in nasal mucosal biopsy specimens of patients with NARES. Patients are typically middle-aged adults. The prevalence of NARES in the general population is uncertain, but NARES occurs extremely infrequently in childhood and probably accounts for less than 2% of children with nasal eosinophilia.¹⁸ It has been proposed that the syndrome might be an early stage of nasal polyposis and aspirin

TABLE II. Differential diagnosis of rhinitis: Conditions that might mimic symptoms of rhinitis

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| A. Nasal polyps |
| B. Structural/mechanical factors |
| 1. Deviated septum/septal wall anomalies |
| 2. Adenoidal hypertrophy |
| 3. Trauma |
| 4. Foreign bodies |
| 5. Nasal tumors |
| a. Benign |
| b. Malignant |
| 6. Choanal atresia |
| 7. Cleft palate |
| 8. Pharyngeal reflux |
| 9. Acromegaly (excess growth hormone) |
| C. Cerebrospinal fluid rhinorrhea |
| D. Ciliary dyskinesia syndrome |

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sensitivity.¹⁹ Patients with NARES are at risk for obstructive sleep apnea.²⁰

Hormonal rhinitis and rhinitis of pregnancy. Rhinitis can be caused by hormonal changes of pregnancy or puberty, the use of oral contraceptives or conjugated estrogens, or thyroid disorders. In *pregnancy rhinitis de novo* nasal congestion develops during pregnancy proposed to occur from hormone-induced nasal vascular pooling resulting from vasodilation and increased blood volume. Symptoms usually disappear within 2 weeks after delivery. However, pre-existing rhinitis is a more common cause of nasal symptoms in pregnant women, with approximately one third of woman with allergic rhinitis having worsened symptoms during pregnancy.²¹

Drug-induced rhinitis. Rhinitis can be caused by either oral or topical medications. Causal oral medications include angiotensin-converting enzyme inhibitors (which can cause nasal symptoms in the absence of the more common adverse effect of cough), β -blockers, various antihypertensive agents, aspirin, other nonsteroidal anti-inflammatory drugs, and oral contraceptives.^{1,2} Use of topical α -adrenergic decongestant sprays for more than 5 to 7 days can induce rebound nasal congestion on withdrawal and reduced mucociliary clearance because of loss of ciliated epithelial cells (rhinitis medicamentosa).²² Repeated use of intranasal cocaine and methamphetamine can also result in rebound congestion and, on occasion, septal erosion and perforation.

Food-induced rhinitis. Ingested food allergens rarely cause isolated rhinitis on an IgE-mediated basis without involvement of other organ systems.^{1,2} Ethanol in beer, wine, and other alcoholic drinks can produce symptoms that have been proposed to occur because of pharmacologic nasal vasodilation. Gustatory rhinitis is a cholinergically mediated syndrome of watery rhinorrhea occurring immediately after ingestion of foods, particularly hot and spicy foods.²³ It can occur as a distinct entity or accompany other types of rhinitis.

Atrophic rhinitis. Primary atrophic rhinitis is a chronic condition characterized by progressive atrophy of the nasal mucosa, resorption of underlying bone and turbinates, nasal dryness, and foul-smelling nasal crusts associated with a constant bad smell (ozena).^{24,25} Often associated with sinusitis, it occurs more commonly in young to middle-aged adults and is more prevalent in developing countries with warm climates. The nasal cavities appear abnormally wide on examination, and squamous metaplasia,

atrophy of glandular cells, and loss of pseudostratified epithelium are found in nasal biopsy specimens. The dryness and reduction of nasal mucosal tissue with the resultant decreased resistance to airflow is, paradoxically, perceived by patients as severe nasal congestion. An infectious basis has been proposed. Secondary atrophic rhinitis can be less severe and progressive than primary atrophic rhinitis and develops as a direct result of other primary conditions, such as chronic granulomatous nasal infections, chronic sinusitis, excessive nasal surgery, trauma, and irradiation.

Infectious rhinosinusitis. Acute viral upper respiratory tract infection (URI) presents with nasal symptoms and constitutional symptoms (fever, myalgias, and malaise). Pruritus is typically absent, and symptoms resolve within 7 to 10 days. Acute and chronic bacterial sinusitis can be difficult to distinguish from rhinitis on the basis of history (see the section on infectious rhinosinusitis).

Differential considerations other than rhinosinusitis

For more information on differential considerations other than rhinosinusitis, see Table II. Anatomic abnormalities usually present with prominent obstructive symptoms with less prominent symptoms of rhinorrhea. Septal deviation can cause symptoms of unilateral or bilateral congestion or recurrent sinusitis, although more often it is asymptomatic. Septal deviations can often be diagnosed by seeing the external deviation of the nose or by looking anteriorly with a nasal speculum. Diagnosis might require fiberoptic rhinopharyngoscopy or computed tomographic (CT) scanning. Nasal polyps are benign inflammatory growths that arise from the inflamed mucosa lining the paranasal sinuses. They can cause invariant unilateral or bilateral nasal obstruction and loss of smell or rhinorrhea (see the section on CRS with nasal polyposis [CRS_{NP}]). Polyps are infrequent in children, except for those with cystic fibrosis, in whom polyps with neutrophilic infiltrates are characteristic,²⁶ in contrast to eosinophilic infiltrates typical of most nasal polyps. Unilateral nasal polyps should raise consideration of a possible neoplasm.

Other differential considerations for nasal symptoms include nasal tumors that can be benign or malignant. The most common presentation of tumors is obstruction. Juvenile angiofibromas often present with bleeding in adolescent males. Nasal carcinoma can present with unilateral epistaxis and nasal pain. Young children might place intranasal foreign bodies in their noses (eg, small parts of toys), leading to foul-smelling, purulent discharge and unilateral nasal obstruction that predisposes to sinusitis. Adenoidal hypertrophy in young children causes bilateral nasal obstruction and is often associated with nocturnal mouth breathing and snoring. Wegener granulomatosis can present with nasal and sinus complaints, including purulent rhinorrhea and occasionally septal erosions and perforations. Sjögren syndrome can cause nasal dryness, congestion, and crusting. Sarcoidosis can present with nasal congestion.

Diagnosis. Full evaluation of a patient with rhinitis should include assessment of specific symptoms bothersome to the patient (eg, nasal congestion, pruritus, rhinorrhea, and sneezing), the pattern of symptoms (eg, infrequent/intermittent, seasonal, and perennial) that might affect therapeutic choices, identification of precipitating factors that might be avoided, previous response to medications, coexisting conditions, and a detailed environmental history, including home and occupational exposures.^{1,2} Nasal itching is more suggestive of allergic rhinitis than nonallergic rhinitis. Because allergic rhinitis is frequently associated with

allergic conjunctivitis, the presence of eye pruritus and lacrimation is a helpful indication that a patient's rhinitis has an allergic basis. Pollens are generally associated with seasonal allergic rhinitis. In most regions of the United States, trees pollinate in the spring, grasses in the late spring and early summer, and weeds in the late summer and fall. However, in some regions (eg, portions of California) pollens can cause perennial symptoms. Perennial allergens, such as house dust mites, cockroaches, and animals, cause symptoms that vary little between seasons, making it difficult to accurately distinguish between allergic and nonallergic rhinitis on the basis of history alone. Family history is an important clue in making the diagnosis of allergic rhinitis in children. A handheld otoscope or headlamp with nasal speculum permits viewing of the anterior third of the nasal airway, including the anterior tip of the inferior turbinates (and occasionally the anterior tip of the middle turbinates) and portions of the nasal septum. Treatment with a topical decongestant improves visualization of the nasal cavity. However, some nasal polyps, septal deviation, and masses can be missed because of the inability to visualize the posterior and superior nasal airways. Typically, patients with allergic rhinitis have clear discharge, swollen turbinates, and bluish or pale mucosa. Pale or erythematous mucosa can be seen in various types of nonallergic rhinitis. Both allergic and nonallergic rhinitis can cause *allergic shiners*, infraorbital darkening thought to be caused by chronic venous pooling, or an *allergic salute* in children who rub their noses upward because of nasal discomfort, sometimes producing a persistent horizontal crease across the nose. In association with rhinitis, physical findings of bilateral conjunctivitis (mild injection with nonpurulent discharge) are suggestive of allergy. Patients with nasal disease require appropriate examination for associated diseases, such as sinusitis and otitis media.

Determination of specific IgE antibodies to known allergens by means of skin testing or *in vitro* tests is indicated to provide evidence of an allergic basis for the patient's symptoms, to confirm or exclude suspected causes of the patient's symptoms, or to assess the sensitivity to a specific allergen for avoidance measures, allergen immunotherapy, or both.^{1,2} Skin testing is preferred for its simplicity, ease, and rapidity of performance; low cost; and high sensitivity.¹ In patients with perennial rhinitis, history is usually insufficient for distinguishing allergic from nonallergic rhinitis, and testing is of added importance. Neither total serum IgE levels nor total circulating eosinophil counts are routinely indicated in the diagnosis of rhinitis because they are neither sensitive nor specific for allergic rhinitis.¹

Nasal cytology might aid in differentiating allergic rhinitis and NARES from other forms of rhinitis, such as vasomotor or infectious rhinitis, if the correct procedure is followed and the appropriate stains are used. However, there is lack of expert consensus about whether nasal cytology should be routinely used in the diagnosis of rhinitis.¹ In selected cases special techniques, such as fiberoptic nasal endoscopy, inspiratory peak flow measurements, acoustic rhinometry, or rhinomanometry, to assess airway function might be useful in evaluating patients presenting with rhinitis symptoms.

Treatment. Avoidance measures. Avoidance of inciting factors, such as allergens (house dust mites, molds, pets, pollens, and cockroaches), irritants, and medications, can effectively reduce symptoms of rhinitis. In particular, patients allergic to house dust mites should use allergen-impermeable encasings on the bed and all pillows. Pollen exposure can be reduced by

keeping windows closed, using an air conditioner, and limiting the amount of time spent outdoors.

Medications. Selection of medications should be individualized based on multiple considerations, including patient preference (eg, intranasal vs oral), individual response (which can differ from average responses in the general population), and cost.¹ Some medications are more effective for treating certain types of rhinitis (eg, allergic vs nonallergic), more severe symptoms, or particular rhinitis symptoms that are more bothersome to a patient (eg, nasal congestion).^{1,2} Medications also differ in onset of action, with those having more rapid symptom relief better suited to treating episodic rhinitis (defined by the Joint Task Force as allergic nasal symptoms elicited by sporadic exposures to inhaled aeroallergens that are not usually encountered in the patient's indoor or outdoor environment)¹ or intermittent symptoms (defined by Allergic Rhinitis and Its Impact on Asthma guidelines as present <4 days per week or <4 weeks duration).² Table III reviews principal medication options for rhinitis (both monotherapy and combination regimens), listing therapeutic considerations for treatment of allergic rhinitis and then for nonallergic rhinitis.

Allergen immunotherapy/allergy vaccination. Subcutaneous allergen immunotherapy can be highly effective in controlling symptoms of allergic rhinitis and favorably modifies the long-term course of the disease.²⁷ Sublingual immunotherapy with single allergens, although part of clinical practice for the treatment of rhinitis in Europe, is undergoing clinical trials in the United States and is not approved by the US Food and Drug Administration (FDA) at the time of this manuscript's submission. Patients with allergic rhinitis should be considered candidates for immunotherapy on the basis of the severity of their symptoms, failure or unacceptability of other treatment modalities, presence of comorbid conditions, and possibly as a means of preventing worsening of the condition or the development of comorbid conditions (eg, asthma and sinusitis).^{1,27} Approximately 80% of patients will experience symptomatic improvement after 1 to 2 years of subcutaneous immunotherapy, and guidelines recommend that treatment be continued for a total of 4 to 5 years.²⁷ In many patients the beneficial effects persist for years after injections are stopped. Allergen immunotherapy for allergic rhinitis can reduce the development of asthma in children and possibly in adults.^{1,27,28}

Considerations in select populations. Children. Because some, although not all, nasal corticosteroid preparations have been reported to reduce linear growth (at least temporarily),²⁹⁻³¹ growth should be monitored in children receiving these agents.

Elderly. Allergy is an uncommon cause of perennial rhinitis in individuals older than 65 years. More commonly, rhinitis in the elderly is due to cholinergic hyperreactivity (associated with profuse watery rhinorrhea, which might be aggravated after eating [ie, gustatory rhinitis]), α -adrenergic hyperactivity (congestion associated with antihypertensive drug therapy), or sinusitis.¹ Because the elderly might have increased susceptibility to the adverse central nervous system and anticholinergic effects of antihistamines, non-sedating agents are recommended if antihistamines are used for allergic rhinitis. Oral decongestants should be used with caution in this patient subset because of their effects on the central nervous system, heart, and bladder function.

Pregnancy. The time for greatest concern about potential congenital malformation caused by medication use is the first trimester, when organogenesis occurs.^{1,32,33} When selecting medications for treating rhinitis in pregnancy, the clinician might

TABLE III. Principal medication options for rhinitis (listed in alphabetical order)

| For AR, both seasonal and perennial | |
|--|---|
| | Therapeutic considerations |
| Monotherapy | |
| Oral agents | |
| Antihistamines, oral (H1 receptor antagonists) | <ul style="list-style-type: none"> ● Continuous use is most effective for SAR and PAR but appropriate for PRN use in episodic or intermittent AR because of relatively rapid onset of action. ● Less effective for nasal congestion than for other nasal symptoms ● Less effective for AR than INSs, with similar effectiveness to INSs for associated ocular symptoms ● Because they are generally ineffective for non-AR, other choices are typically better for mixed rhinitis. ● To avoid sedation (often subjectively unperceived), performance impairment, or anticholinergic effects of first-generation antihistamines, second-generation agents are generally preferred. ● Of these, fexofenadine, loratadine, and desloratadine without sedation at recommended doses |
| Corticosteroids, oral | <ul style="list-style-type: none"> ● A short course (5-7 days) might be appropriate for very severe nasal symptoms. ● Preferred to single or recurrent administration of intramuscular corticosteroids |
| Decongestants, oral | <ul style="list-style-type: none"> ● Pseudoephedrine reduces nasal congestion. ● Side effects include insomnia, irritability, palpitations, and hypertension. |
| Leukotriene receptor antagonists (LTRAs) | <ul style="list-style-type: none"> ● Montelukast is approved for SAR and PAR. ● The efficacies of LTRAs and oral antihistamines are similar (with loratadine as the usual comparator). ● Because approved for both rhinitis and asthma, can be considered when both conditions are present. ● Side effects are minimal. |
| Intranasal agents | |
| Intranasal antihistamines | <ul style="list-style-type: none"> ● Effectiveness for AR is equal or superior to that of oral second-generation antihistamines with a clinically significant effect on nasal congestion. ● Generally less effective than INSs for nasal symptoms ● Clinically significant rapid onset of action (within several hours or less), making them appropriate for PRN use in patients with episodic AR ● Because azelastine nasal spray is approved for vasomotor rhinitis, appropriate choice for mixed rhinitis ● Side effects with intranasal azelastine are bitter taste and somnolence. |
| Intranasal anticholinergic (ipratropium) | <ul style="list-style-type: none"> ● Reduces rhinorrhea but not other symptoms of AR. ● Appropriate for episodic AR because of rapid onset of action ● Side effects are minimal, but nasal dryness can occur. |
| Intranasal corticosteroids (INSs) | <ul style="list-style-type: none"> ● Most effective monotherapy for AR ● Effective for all symptoms of SAR and PAR, including nasal congestion ● The usual onset of action is less rapid than that of oral or intranasal antihistamines, usually occurs within 12 hours, and can start as early as 3-4 hours in some patients. ● Might be considered for episodic AR ● PRN use (eg, >50% days use) is effective for SAR. ● More effective than the combination of an oral antihistamine and LTRA for SAR and PAR ● Similar effectiveness to oral antihistamines for associated ocular symptoms of AR ● Appropriate choice for mixed rhinitis because agents in this class are also effective for some cases of non-AR ● Without significant systemic side effects in adults ● Growth suppression in children with PAR has not been demonstrated when used at recommended doses. ● Local side effects are minimal, but nasal bleeding can occur, as well as rare nasal septal perforation. |
| Intranasal cromolyn | <ul style="list-style-type: none"> ● Used for maintenance treatment of AR; onset of action within 4-7 days; full benefit can take weeks. ● For episodic rhinitis, administration just before allergen exposure protects for 4-8 hours against allergic response. ● Less effective than nasal corticosteroids, and there are inadequate data for comparison with leukotriene antagonists and antihistamines. ● Minimal side effects |
| Intranasal decongestants | <ul style="list-style-type: none"> ● Useful for the short-term and possibly for episodic therapy of nasal congestion but inappropriate for daily use because of risk for rhinitis medicamentosa |

(Continued)

TABLE III. (Continued)

| Therapeutic considerations | |
|---|--|
| Combination therapy | |
| Antihistamine, oral with decongestant, oral | ● Provides more effective relief of nasal congestion than antihistamines alone |
| Antihistamine, oral with LTRA, oral | ● Might be more effective than monotherapy with an antihistamine or LTRA |
| | ● Combination is less effective than INSs. |
| | ● Alternative if patients are unresponsive to or not compliant with INSs |
| Antihistamine, oral with intranasal antihistamine | ● Combination can be considered, although controlled studies of additive benefit are lacking. |
| Antihistamine, oral with INS | ● Combination can be considered, although supporting studies are limited, and many studies are unresponsive of the additive benefit of adding an antihistamine to an intranasal steroid. |
| Intranasal anticholinergic with INS | ● Concomitant ipratropium bromide nasal spray with INS is more effective for rhinorrhea than administration of either drug alone. |
| Intranasal antihistamine with INS | ● Combination can be considered based on limited data indicating additive benefit. |
| | ● There are inadequate data about the optimal interval between administration of the 2 sprays. |
| | ● For mixed rhinitis, there is a possible added benefit to combination of intranasal antihistamine with INS. |
| LTRA, oral with INS | ● Provides subjective additive relief in limited studies; data are inadequate. |
| For nonallergic (idiopathic) rhinitis | |
| Therapeutic considerations (for side effects, see AR table) | |
| Monotherapy | |
| Oral agents | |
| Antihistamines, oral (H1 receptor antagonists) | ● Generally ineffective for non-AR |
| Decongestants, oral | ● Pseudoephedrine reduces nasal congestion. |
| Intranasal agents | |
| Intranasal antihistamines | ● Effective for vasomotor rhinitis |
| Intranasal anticholinergic (ipratropium) | ● Effective only for rhinorrhea of non-AR syndromes |
| | ● Special role for preventing rhinorrhea of gustatory rhinitis |
| INSs | ● Effective for some forms of non-AR, including vasomotor rhinitis and NARES |
| Combination therapy | ● There are inadequate data to provide firm recommendations in non-AR. |

Adapted from Wallace et al.¹

AR, Allergic rhinitis; INS, intranasal corticosteroids; LTRA, leukotriene receptor antagonist; PAR, perennial allergic rhinitis; PRN, as required; SAR, seasonal allergic rhinitis.

consider the FDA risk categories (category B being more favorable than category C) that are based largely on animal data and limited human studies.¹ However, it is also suggested that a clinician consider human cohort and case-control studies, as well as birth registry data.¹ Nasal cromolyn has the most reassuring safety profile in pregnancy. Cetirizine, chlorpheniramine, loratadine, and triptolennamine have been rated FDA pregnancy category B, whereas many other antihistamines have a category C rating. Intranasal budesonide has a category B rating, whereas other nasal corticosteroids are rated category C. Oral decongestants are best avoided in the first trimester because of the risk of gastroschisis in the newborn.³⁴ Allergen immunotherapy should not be started or advanced in dose during pregnancy but might be continued at a stable dose.

SINUSITIS (RHINOSINUSITIS)

Sinus anatomy and physiology

Normal sinus function requires (1) patency of each sinus ostia, (2) normal mucociliary function, and (3) normal systemic and local immune function. Epithelial cilia in the sinuses normally beat mucus in an ordered fashion toward the ostia that communicate with the nasal cavity. The maxillary, anterior ethmoid, and frontal sinuses drain through a comparatively narrow drainage pathway, the ostiomeatal unit (complex), which communicates into the middle meatus, a space between the inferior and middle turbinates (Fig 2). In 50% of cases, the frontal sinus drains just anterior to this region. The posterior ethmoid and sphenoid sinuses

drain through the sphenoethmoidal recess. Sinus ostial obstruction is common in patients with acute rhinosinusitis and CRS. Mucociliary function is grossly abnormal in diseases, such as cystic fibrosis, or in ciliary dysmotility syndrome (Kartagener syndrome). Mucociliary function might be impaired by cigarette smoke, environmental pollutants, or viral URIs.³⁵ Systemic immune function is impaired by hypogammaglobulinemia, severe T-cell dysfunction, or immune suppression. It has been suggested but not proved that defects in local innate immune function might predispose to sinus infections. Local innate function involves (1) pathogen recognition and signaling through epithelial Toll-like and other innate receptors and (2) secretion of collectins and antimicrobial peptides.³⁶ Defects in either pathway remain largely unstudied in sinusitis.

Rationale for rhinosinusitis rather than sinusitis

The symptoms of rhinitis and sinusitis overlap, and sinusitis rarely occurs in the absence of rhinitis.⁴ Second, there is an important interrelationship between the middle turbinate and the ethmoid sinus such that cyclic variations in nasal turbinate swelling occurring during the normal nasal cycle can cause mucosal thickening in the ethmoidal infundibulum. This thickening might be interpreted as ethmoid sinusitis.³⁷ The ethmoid infundibulum and the nose represent contiguous structures sharing vascular, neuronal, and interconnecting anatomic pathways. For these reasons, some expert panels have adopted the term

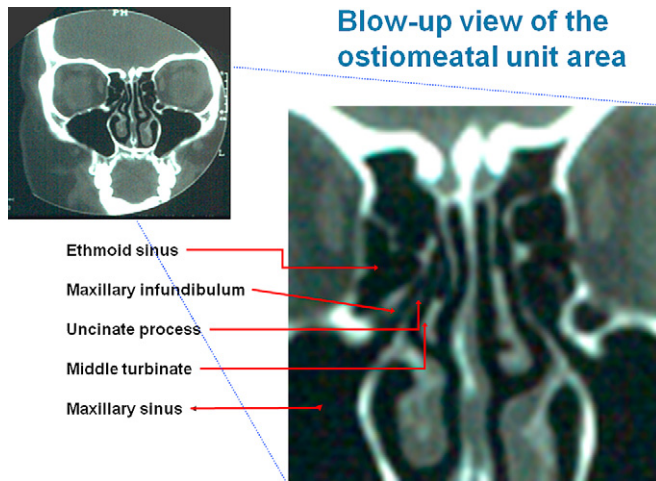


FIG 2. The ostiomeatal unit is well visualized on this blow-up of a normal sinus CT scan. The major structures illustrated include the maxillary infundibulum, the ethmoid infundibulum, the uncinate process, and the middle turbinate. The ostiomeatal unit is a 3-dimensional structure made up of these individual components.

rhinosinusitis rather than sinusitis, emphasizing that sinusitis typically involves the nasal passages and the paranasal sinuses.^{4,38} For the purposes of this review, sinusitis and rhinosinusitis are synonymous terms.

Infectious rhinosinusitis

Viral rhinosinusitis is defined as acute rhinosinusitis caused by viral infection. Viral rhinosinusitis is often difficult to distinguish from acute bacterial rhinosinusitis (ABRS) and can be accompanied by inflammatory changes in the sinuses.³⁹ ABRS, by definition, is caused by a bacterial pathogen. CRS is an inflammatory condition in which infection plays an important role. Each of these entities is discussed further below.

The transition from viral rhinosinusitis to ABRS

The principal inciting event for ABRS is viral rhinosinusitis (also known as a viral URI). The transition from viral rhinosinusitis to ABRS is variable and only occurs in 0.5% to 2% of cases.³⁹ Viral rhinosinusitis is typically accompanied by clear rather than thick or colored secretions. Symptoms can persist up to 14 days or longer. An acute upper respiratory illness of less than approximately 7 days' duration is most commonly caused by viral illness (viral rhinosinusitis), whereas acute bacterial sinusitis becomes more likely beyond 7 to 10 days.^{3,4} Transition from viral URI to ABRS can occur at any time during the viral URI.⁴⁰

Acute and chronic rhinosinusitis: Definitions and symptoms

Rhinosinusitis is defined as inflammation of the nose and paranasal sinuses. Acute rhinosinusitis is usually infectious, whereas CRS is less clearly infectious and often more inflammatory.⁴ However, infection still plays an important role in CRS. *Acute rhinosinusitis* is defined as up to 4 weeks of purulent (not clear) nasal drainage (anterior, posterior, or both) accompanied by nasal obstruction, facial pain-pressure-fullness, or both. *Subacute*

rhinosinusitis is defined in some expert reports³ as rhinosinusitis of between 4 and 8 weeks' duration. CRS is defined as an inflammatory condition involving the paranasal sinuses and nasal passages with a minimum duration of either 8 or 12 weeks despite attempts at medical management.^{3,4}

The 4 major symptoms of CRS are (1) anterior, posterior, or both mucopurulent drainage; (2) nasal obstruction or blockage; (3) facial pain, pressure, and/or fullness; and (4) decreased sense of smell. Two or more symptoms must be present to make the diagnosis.^{4,41} In addition, objective documentation of mucosal inflammation is required.

The symptoms of CRS do not reliably correlate with specific objective findings nor do they accurately differentiate CRS subtypes (see below).

Facial pain, pressure, and/or headache are commonly reported symptoms (83% in one series).⁴² The pain is usually described as a dull pain or pressure in the upper cheeks, between the eyes, or in the forehead. Sharp localizing pain is less common. Anterior, posterior, or both nasal drainage of CRS is usually opaque white or light yellow. Thick yellow, green, or brown mucus can occur, although this is more characteristic of recurrent acute rhinosinusitis or AFRS. Nasal congestion can be described as nasal blockage or stuffiness or less commonly as nasal fullness. Disturbance in sense of smell can be partial (hyposmia) or complete (anosmia) and is usually associated with mucosal thickening or opacification in the anterior ethmoid sinuses. Rarely, hyposmia/anosmia is caused by olfactory neuronal degeneration or other diseases. Patients with anosmia often report ageusia, a reduced ability to taste foods.

There is a poor correlation between the symptoms of CRS and objective findings on imaging of the paranasal sinuses.^{43,44}

Differential considerations other than rhinitis

Facial pain can be caused by nonrhinogenic conditions, including migraine headaches, tension headaches, cluster headaches, and other poorly understood facial pain syndromes.^{45,46} Facial pain, pressure, or both are not reliable for predicting the presence of objective findings of rhinosinusitis.⁴⁶ Focal and sharp facial pain might be a symptom of CRS but is often not associated with radiographic evidence of sinus disease. Pain in the upper teeth, which is suggestive of nerve irritation in adjacent tooth roots, can be a symptom of maxillary sinus infection.

The differential diagnosis of nasal congestion includes allergic rhinitis, chronic nonallergic (idiopathic) rhinitis, rhinitis associated with medication use, secondary atrophic rhinitis (ie, empty nose syndrome), and cerebrospinal fluid rhinorrhea. Unilateral nasal congestion/blockage raises the question of a local anatomic problem, such as an antral choanal cyst, or tumor, such as an inverted papilloma.⁴⁷

Subtypes of CRS

CRS can be divided into 3 clinical subtypes with distinctive but overlapping clinical features (Table IV).

1. CRS without nasal polyposis (CRSsNP) accounts for approximately 60% of CRS cases. It is a heterogeneous condition in which allergic factors, structural abnormalities, and viral and bacterial infection variably contribute to the disease. Facial pain, pressure, and/or fullness are more common in CRSsNP than in CRSwNP (see below). Bacterial organisms isolated from diseased sinus cavities

can include: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, coagulase-negative staphylococci, and, less commonly, gram-negative enteric bacteria. The importance of anaerobic bacteria in causing CRS is controversial.⁴ Sinus ostial blockage is the inciting event, in most cases leading to obstruction of sinus drainage and bacterial infection. As the condition becomes chronic, a chronic inflammatory infiltrate containing neutrophils, mononuclear cells, and some eosinophils is seen. Glandular hyperplasia and submucosal fibrosis are typically present histologically in patients with CRSsNP but absent in patients with CRSsNP.^{48,49}

2. CRSsNP accounts for 20% to 33% of CRS cases. The symptoms are similar to those of CRSsNP, although hyposmia/anosmia is more common in patients with CRSsNP.⁵⁰ Nasal polyps are typically bilateral in the middle meatus unless they have been previously removed. Unilateral polyps are relatively uncommon and should prompt consideration of other diagnoses, including inverted papilloma or other nasal tumors. CRSsNP is more likely than CRSsNP to be associated with asthma and aspirin-exacerbated respiratory disease (AERD). The initial trigger for nasal polyp development is unknown. Polyp tissue typically contains a predominance of eosinophils, high levels of histamine, and high levels of the T_H2 cytokines IL-5 and IL-13.^{51,52}
3. AFRS is defined as CRS accompanied by (1) the presence of allergic mucin (thick inspissated mucus that ranges in color from light tan to brown to dark green and that contains degranulated eosinophils), (2) fungal hyphae in the mucin, and (3) evidence of IgE-mediated fungal allergy.⁴ Allergic mucin is thick inspissated mucus that ranges in color from light tan to brown to dark green and that contains degranulated eosinophils. Sinus surgery is usually required to remove allergic mucin and establish the diagnosis of AFRS. Fungal hyphae are found within the allergic mucin, suggesting fungal colonization. The fungi are strictly noninvasive. Patients with AFRS usually have nasal polyps and are immunocompetent. Symptoms are similar to those of other forms of CRS. Fever is uncommon. Occasionally, AFRS presents dramatically with complete nasal obstruction, gross facial dysmorphism, and/or visual changes.⁴ The pathophysiology of AFRS is most consistent with chronic, intense allergic inflammation directed against colonizing fungi. Histologically, allergic mucin demonstrates intense eosinophilic degranulation, mucostasis, and inspissations.⁵³

Distinct pathologic features of rhinosinusitis

Allergic mucin. Allergic mucin is a classic feature of AFRS.^{54,55} However, allergic mucin is occasionally found in the absence of colonizing fungi in some cases of CRSsNP or CRSsNP.

Hyperdensities on sinus CT scanning. Opacified sinus cavities might contain inspissated mucus that produces an inhomogeneous hyperdense pattern on sinus CT scanning. Hyperdensities suggest the presence of allergic mucin. They are a classic feature of AFRS (in which case the allergic mucin also contains fungal hyphae), but they can be seen in both CRSsNP and CRSsNP.

TABLE IV. Definitions of rhinosinusitis based on disease classification

| |
|--|
| Recurrent acute rhinosinusitis |
| A. Recurrent acute rhinosinusitis >3 times per year |
| B. Requires >2 of the following symptoms: |
| • Anterior or posterior mucopurulent drainage |
| • Nasal congestion |
| • Facial pain/pressure |
| • Decreased sense of smell |
| C. Normal between episodes |
| Chronic rhinosinusitis with nasal polyps |
| A. Symptoms present for >12 weeks |
| B. Requires >2 of the following symptoms: |
| • Anterior or posterior mucopurulent drainage |
| • Nasal congestion |
| • Facial pain/pressure |
| • Decreased sense of smell |
| C. Objective documentation |
| • Rhinoscopic examination OR |
| • Radiograph (sinus CT scan preferred) |
| D. Bilateral nasal polyps in middle meatus |
| Chronic rhinosinusitis without nasal polyps |
| A. Symptoms present for >12 weeks |
| B. Requires >2 of the following symptoms: |
| • Anterior or posterior mucopurulent drainage |
| • Nasal congestion |
| • Facial pain/pressure |
| • Decreased sense of smell |
| C. Objective documentation |
| • Rhinoscopic examination OR |
| • Radiography (sinus CT preferred) |
| AFRS |
| A. Symptoms present for >12 weeks |
| B. Requires >2 of the following symptoms: |
| • Anterior or posterior mucopurulent drainage |
| • Nasal congestion |
| • Facial pain/pressure |
| • Decreased sense of smell |
| C. Objective documentation |
| • Rhinoscopic examination OR |
| • Radiography (sinus CT scan preferred) |
| D. AFRS criteria |
| • Positive fungal stain or culture of allergic mucin AND |
| • IgE-mediated fungal allergy |

A potential role for colonizing fungi in CRS. Patients with CRS (including those with CRSsNP and CRSsNP) have been found to have immune hypersensitivity to fungi, such as *Alternaria* species, that commonly colonize sinus mucus.^{56,57} Although most patients do not produce a classic IgE-mediated response against these fungi, eosinophilic inflammation caused by a T_H2-type sensitization is present. The T-cell cytokines involved include IL-5 and IL-13. The eosinophilic inflammation is most intense in the mucus, where the eosinophils physically associate with fungal hyphae.⁵⁸

Role of bacterial infection. CRS is a complex inflammatory disorder rather than a simple infectious process. Bacterial infections can complicate all forms of CRS. Bacteria can be involved in the pathogenesis of CRS, in the following ways:

- ABRS might fail to resolve, leading to a chronic infection in 1 or more sinuses.
- Bacterial colonization with enterotoxin-producing *S aureus* is found with increased prevalence in patients with

CRScNP and is associated with local production of enterotoxin-specific IgE antibodies.^{59,60} These antibodies can be measured in sinus tissues, although levels in the blood might be undetectable. The enterotoxins act as superantigens and locally activate T lymphocytes.⁵⁹ In contrast, patients with CRSsNP do not have an increased prevalence of enterotoxin-specific IgE antibodies.

- Bacteria can form biofilm on the sinus epithelium. Sequestration of bacteria within biofilms allows the bacteria to resist antibiotic treatment and persist as a low-grade infection within the sinus mucosa.^{61,62}
- Drug-resistant infection can occur with gram-negative bacteria or methicillin-resistant *S aureus*.⁴¹
- Acute bacterial infection can lead to osteitis of the underlying bone, although actual invasion of the bone has not been conclusively demonstrated.⁶³

Physical findings

The diagnosis of ABRS requires the presence of purulent nasal discharge (secretions that are cloudy or colored) and nasal obstruction (congestion, blockage, or stuffiness), facial pain-pressure-fullness, or both.⁴⁰ Using a positive sinus radiograph as a gold standard for confirmation of disease, this symptom definition only allows for correct diagnosis in approximately 40% to 50% of cases.⁶⁴ Nonetheless, ABRS remains a clinical diagnosis.

The definitive diagnosis of CRS requires objective confirmation of disease either with nasal endoscopy or sinus CT scanning. Nasal endoscopy might reveal discolored mucus or edema in the middle meatus or sphenoethmoidal recess or similar findings in the sinus cavities of patients who have undergone previous surgery. Typical findings on sinus CT include sinus ostial narrowing or obstruction, sinus mucosal thickening or opacification, and, less commonly, air-fluid levels in the sinuses.

Diagnostic testing

Sinus imaging with plain radiography or sinus CT scanning is not recommended in patients with uncomplicated ABRS unless symptoms or signs suggesting extrasinus involvement are present.⁴⁰ Sinus CT scanning is the imaging study of choice for evaluation of CRS.^{4,40} Coronal images are commonly obtained, although multiplanar images are available in many institutions. Nasal endoscopy is sufficient to establish the diagnosis of CRS but is insufficient to establish the extent of sinus involvement unless extensive prior sinus surgery has been performed.

Because CRS is associated with allergic rhinitis in 60% of adults and 36% to 60% of children, patients with CRS should be evaluated for allergy so that environmental control measures or other interventions appropriate for allergic disease can be implemented.³

Initial treatment of ABRS

An initial period of watchful waiting without initiation of antibiotics can be considered in adults with uncomplicated ABRS who have mild illness (mild pain and temperature <38.3 °C) and assurance of follow-up.⁴⁰ Spontaneous resolution has been reported in 62% to 69% of patients in placebo-controlled clinical trials.⁴⁰ Patients with more severe symptoms should be treated with an antibiotic. The most common bacteria isolated from the maxillary sinuses of patients with ABRS include *S pneumoniae*, *H influenzae*, and *M catarrhalis*, the latter

being more common in children.⁴⁰ If a decision is made to treat with an antibiotic, amoxicillin is considered first-line therapy for most adults. For patients with penicillin allergy, trimethoprim-sulfamethoxazole or macrolide antibiotics are cost-effective alternatives. Several additional antibiotics, including cephalosporins and fluoroquinolones, are FDA approved for treatment of ABRS.

Intranasal decongestants might relieve nasal congestion but should be limited to 3 days to avoid rebound nasal congestion.⁴⁰ Intranasal corticosteroid sprays have been studied but are not approved as adjunctive therapy.

When initial therapy of ABRS fails

If ABRS does not improve after several days of antibiotics, prescription of an alternative antibiotic for several additional weeks should be considered.³ If there is still no response, a sinus CT scan is indicated to confirm the presence of sinusitis and determine whether anatomic abnormalities might be predisposing to sinusitis. Underlying medical conditions should also be considered, including immune deficiency, gastroesophageal reflux disease, or defects in mucociliary clearance (see the section on chronic rhinosinusitis comorbidities). Specialist evaluation is appropriate when sinusitis is refractory to treatment or is recurrent.

Findings that suggest need for immediate referral

The following symptoms and signs are suggestive of other conditions that require immediate evaluation: double or reduced vision, proptosis, dramatic periorbital edema, ophthalmoplegia, other focal neurologic signs, severe headache, and meningeal signs.⁶⁵ Extrasinus extension of sinus disease is the most ominous complication of acute rhinosinusitis or CRS. Complications of acute sinusitis include orbital cellulitis, cavernous vein thrombosis, brain abscess, meningitis, localized osteomyelitis, and oral-antral fistula. Complications of chronic sinusitis include localized osteomyelitis, oral-antral fistula, mucocele, and brain abscess.

Treatment of chronic rhinosinusitis

Topical corticosteroid nasal sprays are recommended for all forms of CRS.⁶⁶ Antihistamines might be helpful in patients with underlying allergic rhinitis.⁶⁶ Antibiotics should be used to treat infection if nasal purulence is present, although antibiotics have not been officially approved for use in CRS. Antifungals, including oral terbinafine and topical amphotericin B, have been studied in patients with CRS.⁶⁷⁻⁶⁹ Most antifungal trials have failed to show efficacy, and antifungal agents are not recommended.

CRScNP. Patients might benefit from a brief course (10-15 days) of oral corticosteroids to shrink nasal polyps.⁷⁰ Topical corticosteroid nasal sprays are recommended.⁷¹ In patients with severe polyposis, sinus surgery with debulking of nasal polyps might be necessary. Topical corticosteroid nasal sprays are recommended to prevent recurrence of nasal polyps, although they are not always effective. Antileukotriene agents (eg, zafirlukast, montelukast, and zileuton) have received limited study and are not FDA approved for the treatment of nasal polyps. Patients with nasal polyps who have AERD might benefit from aspirin desensitization and daily aspirin therapy, provided they have no contraindications to aspirin therapy.⁶⁶

AFRS. Sinus surgery is almost always required to establish the diagnosis of AFRS, remove inspissated mucus, and restore sinus patency. Nearly all patients with AFRS have nasal polyps. After surgery, oral corticosteroids are recommended at 0.5 mg/kg daily, with gradual tapering of the dose to the lowest possible dose necessary to maintain control of sinus symptoms. Topical corticosteroid nasal sprays are also recommended to control inflammation and prevent recurrence of nasal polyps.

Indications for sinus surgery

Functional endoscopic sinus surgery (FESS) is the procedure of choice for surgical management of refractory CRS. FESS is predicated on the observation that CRS “usually starts in the nose and spreads through the ethmoidal prechambers to the frontal and maxillary sinuses, with infections of these latter sinuses thus usually being of secondary nature.”⁷² The principal goal of FESS is to restore patency to the ostiomeatal unit, the key anatomic area of drainage of the maxillary and anterior ethmoid sinuses (Fig 2). A typical FESS procedure includes (on each side) removal of the uncinate process, creation of a widened maxillary antrostomy, an ethmoidectomy, and (in some cases) a sphenoidotomy. Additional goals of FESS might include correction of septal deformities, removal of severe concha bullosa deformity (enlarged middle turbinate containing an air cell), and restoration of patency to the frontal sinus. Several studies have reported a high success rate for FESS in improving the symptoms of CRS.⁷³⁻⁷⁵

The classic indications for FESS include (1) persistence of CRS symptoms despite medical therapy, (2) correction of anatomic deformities believed to be contributing to persistence of disease, and (3) debulking of advanced nasal polyposis.

Comorbidities

Allergic rhinitis. IgE-mediated allergy to environmental allergens is found in 60% of patients with CRS (including CRSsNP and CRSsNP) compared with 30% to 40% for the general population.⁷⁶ Patients with CRS are typically sensitized to perennial rather than seasonal (ie, pollen) allergens.⁷⁶ By definition, all patients with AFRS have IgE-mediated allergy to fungi. Fungal spores can germinate in sinus mucus, thereby increasing the allergenic stimulus.

Histopathologic studies of ethmoidal tissue from patients with CRSsNP and nasal polyps from patients with CRSsNP have shown that patients with CRS with associated allergies have mucosal T_H2 cell infiltration with production of classic T_H2 cytokines, including IL-4, IL-5, and IL-13.^{77,78} This suggests that allergens contribute to chronic allergic sinus inflammation.

Immunodeficiency. Deficient antibody production in response to vaccination or hypogammaglobulinemia is found in approximately 12% of adults with CRSsNP.⁵⁰ Immunodeficiency is rare in patients with CRSsNP or AFRS. Most patients with deficient antibody production or hypogammaglobulinemia have a pattern of recurrent acute episodes of purulent infection. They might also have a history of concomitant pulmonary infections or recurrent otitis media. Although the nasal and sinus epithelium expresses Toll-like and other innate receptors and produces a variety of antimicrobial proteins, such as lactoferrin, lysozyme, defensins, collectins, and cathelicidins, there are limited data about CRS risk in patients with defects in innate immunity.⁷⁹

Gastroesophageal reflux disease. Sinusitis is considered a possible extraesophageal manifestation of gastroesophageal reflux disease. The mechanism is believed to be due to direct reflux of gastric acid into the pharynx and nasopharynx, causing inflammation of the sinus ostium and leading to sinusitis.^{80,81}

Defects in mucociliary clearance. Defects in mucociliary clearance, such as those found in patients with cystic fibrosis and primary ciliary dyskinesia, dramatically increase the risk of CRS.

Viral infections. In a small number of cases, patients appear to have CRS after a period of repeated exposure to viral URIs. This is characteristically seen in patients exposed to health care settings, day care centers, schools, or homes with small children. However, data clearly implicating viral agents in the pathogenesis of CRS are scarce,⁸² and the role of viral infection in patients with CRS is controversial.

Systemic diseases. CRS might be the presenting feature of an underlying systemic illness, such as Wegener granulomatosis or Churg-Strauss vasculitis^{83,84} or, less commonly, sarcoidosis.⁸⁵

Anatomic abnormalities. Several common anatomic variants can be seen in patients with CRS, including nasal septal deviation, concha bullosa deformity, Haller cells, agar nasi cells, and paradoxical curvature of the middle turbinate. However, these abnormalities are also seen in otherwise healthy subjects and are not clearly epidemiologically linked to an increased risk of sinusitis.⁸⁶⁻⁸⁹

Associated conditions

Both asthma and AERD are associated with CRS. Approximately 20% of patients with CRS have concomitant asthma. Conversely, approximately two thirds of asthmatic subjects, including both children and adults, have evidence of chronic sinus mucosal thickening or sinus opacification in cross-sectional studies.⁹⁰ The combination of aspirin sensitivity, asthma, and nasal polyposis is referred to as triad asthma, Samter syndrome, or AERD.^{91,92}

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